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Aspects regarding the implications of *Helicobacter pylori* infections in gastric pathology

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ABSTRACT

The normal microbiota of the upper digestive tract plays an essential role in maintaining homeostasis and a normal development of the digestive tract, but also in angiogenesis, metabolism and immunity. Recent data demonstrate the role of the host microbiota in triggering and evolving various pathologies, including malignancies. H. pylori infection is directly correlated with gastric cancer, but, however, the way through which other intra-gastric bacterial species interfere with the effects of the H. pylori in the development of gastric cancer is still undeclared. The purpose of this minireview was to present the implications of H. pylori infection in gastric pathology, including gastric cancer and lymphoma.

Keywords: *normal microbiota, digestive tract, Helicobacter pylori, pathogenesis.*

1. INTRODUCTION

Normal microbiota is the population of microorganisms associated with the skin and mucous membranes in healthy humans, especially in the digestive tract. Although organisms are sterile during intrauterine life, they are progressively colonized by a large number of microorganisms, whose number is estimated at 10^{14} cells, overcoming the total of human body cells (10^{13}). It has been calculated that the adult human body carries 10^{12} bacteria on the skin, 10^{10} in the oral cavity, and 10^{14} in the gastrointestinal tract [1]. The groups of microorganisms which are predominant in the upper digestive tract are streptococci, staphylococci, *Neisseria sp., Psudomonas aeruginosa, Haemophilus influenzae, Corynebacterium sp., Actinomycetes, Spirochetae, Mycoplasma* sp., while in the intestine predominate the *Enterobacteriaceae* strains *(*mostly *E. coli*, but also *Proteus sp.*), *Enterococcus faecalis, Bacteroides sp., Bifidobacterium bifidum, Lactobacillus sp., Clostridium sp.*and even mycobacteria [2].

2. GASTRIC MICROBIOTA

The gastric microbiota has a density estimated at 10^{3}-10^{5} cells / g of mucosa and is associated with the epithelial surface and is protected from the gastric acid pH by the mucus and bicarbonate secretion. The bacteria found in microbiota are acid-tolerant, i.e. *Lactobacillus* sp. *Streptococcus* sp., *Helicobacter pylori*, the last one being involved in the development of gastritis, gastric and duodenal ulcers and even associated with gastric malignancy [2].

3. THE MICROBIOTA OF THE SMALL INTESTINE

Under normal conditions, the density of small intestine microbiota is limited to 10^{5} cells/ml of intestinal content, and the anaerobic lactobacilli and anaerobic enterococci predominate, being represented by *Lactobacillus* sp., *Enterococcus faecalis, Bifidobacterium* sp., *Bacteroides* sp., *Clostridium* sp., *Candida albicans* [3]. The limiting factors of bacterial multiplication in the small intestine are gastric acidity, intestinal peristalsis that provides relatively rapid transit towards the large intestine, and the existence of substances which inhibit the growth of the microorganisms [4].

4. MICROBIOTA OF THE LARGE INTESTINE

In humans and in most mammals, the microbiota of this segment contains up to several hundred O_2 intolerant bacteria, from which only a few have been cultivated *in vitro* and identified. In terms of cell density, anaerobes predominate about 1000 times in relation to the facultative aerobic bacteria. Allochthonous microorganisms become significant if their density exceeds 10^{6} cells / g of intestinal content[5]. In humans, the number of strictly anaerobic bacteria is over 10^{11} cells/ g (30% of the faecal mass), the most predominant genera and species being*Bifidobacterium* sp., *Bacteroides fragilis, Clostridium perfringens*, Gram-positive anaerobic cocci (*Peptostreptococcus* sp., *Enterococcus* sp.), while the facultative aerobic bacteria represent only up to 4% of the total species (proteolytic coliforms - 0.1-1%, *Pseudomonas* sp., lactobacilli, *Candida* etc.) [6].

5. CLINICAL MANIFESTATIONS OF *H. PYLORI* INFECTION

5.1. Acute gastritis. The presence of *H. pylori* in the stomach is always associated with tissue lesions and histological findings of active and chronic gastritis. In acute gastritis, histologically, *H. pylori* infection causes neutrophilic gastritis and then a gradual inflammation with all types of inflammatory cells, predominantly lymphocytes. Gastric acid secretion is usually reduced, and transient hypocchidia may be caused by a toxic effect of *H. pylori* or inflammatory cytokines such as IL-1 that inhibit acid secretion. Approximately 4 weeks after the initial infection, anti-*H. pylori* antibodies appear in the blood. Clinically, an acute infection with *H. pylori* can be diagnosed by the presence of a positive urea respiratory test and anti-IgG negative antibodies [7].

5.2. Chronic gastritis. In chronic gastritis, an inflammatory infiltrateS with lymphocytes and plasma is present in its own lamina. Active inflammation implies the presence of neutrophils in the glandular layer and at the epithelium surface. Variable classes of active inflammation markers can be detected. Lymphoid aggregates are frequently seen in the mucosa [6].

Chronic gastritis associated with *H. pylori* progresses with two large topographic models with different clinical consequences:i) predominantly antral gastritis, characterized by limited inflammation in the antrum, occuring in peoples who subsequently develop duodenal ulcer; ii) progressive pangastritis or multifocal atrophic gastritis characterized by active infection of the body and gastric anther with the progressive development of gastric atrophy and intestinal metaplasia. Humans infected with *H. pylori* who develop gastric carcinoma and gastric ulcer usually have this model of gastritis [8]. Atrophic gastritis, gastric ulcer and gastric cancer are associated with pangastritis, multifocal gastritis, and acid hyposecretion [9].

5.3. Gastric ulcer. H. pylori is associated in 60-70% cases with stomach ulcers and in70-95% cases with duodenal ulcers. The main elements that highlight the causal role of *H. pylori* are:the presence of infection is a risk factor for the development of ulcers; ulcers do not occur in the absence of infection (unless there are other aetiological factors, such as non-steroidal anti-inflammatory drugs);healing the infection leads to a significant decrease in the recurrence rate of the ulcer (from 80% to 15% in the first year and even less afterwards) [10].

5.4. Duodenal ulcer. The association of gastritis with duodenal ulcer has been known for more than50 years, but the pathogenetic factors that initiated the antral gastric process were not known. It is accepted today that *H. pylori* is the "initiator" of the antral inflammatory process [11].

Research done in the last years has shown the existence of a gastric metaplasia both in healthy people, but especially in patients with duodenal ulcer. Gastric metaplasia consists in the transformation of the intestinal (duodenal) epithelium into gastric epithelium. Histological studies confirmed the presence of the *H. pylori* bacteria in the duodenum, but only in areas with gastric metaplasia. The bacterium seems to be adapted only to the environment created by the gastric mucus. The density of the bacteria increases near the ulcerous lesion. In areas with gastric metaplasia, there is an important neutrophil polymorph nuclear infiltrate, an expression of active inflammation. The so-called "duodenal gastritis" appears, suggesting a link between gastric metaplasia and inflammation [9].

6. IMPLICATIONS OF *HELICOBACTER PYLORI* IN GASTRIC MALIGNANCIES.

In 1994, *H. pylori* was included in Group I of carcinogens by the IARC (International Agency for Research on Cancer) [12]. Gastric cancer is one of the most common malignant diseases worldwide, responsible for one-third of global cancer cases [13]. Malignant gastric processes progress frequently to advanced stages in the absence of obvious symptoms, with late diagnosis and, implicitly, poor prognosis. The complex study of the microbiota composition cannot be achieved by conventional cultivation methods, requiring advanced sequencing technologies to study the relationship between gastric microbiota and the pathogenesis of gastric cancer [14].

The pathogenesis of this disease is a process that takes place in multiple stages influenced by multiple factors involving a large number of complex molecules and complex mechanisms still unclear. However, some studies have focused on finding new ways of early diagnosis of gastric cancer based on gastric microbial composition analysis, but the results obtained so far have not revealed any significant differences from the microbiota of a healthy person or patients with other conditions (e.g., dyspepsia) [15].

Case-control studies have shown that *H. pylori* seropositive is associated with an increased risk of gastric cancer (2.1-16.7 times more than seronegative individuals), *H. pylori* is considered a causative agent of gastric carcinogenesis [16].

H. pylori infections are usually chronic infections that last for many years, acute infections are rarely described. Initially, the infection induces superficial (non-atrophic) gastritis, which may progress from chronic atrophic gastritis, intestinal metaplasia, and dysplasia to gastric cancer. However, only a small number of infected patients will develop gastric cancer (less than 1%) [17].

Most of the knowledge about acute infections is from studies in infantile population. When *H. pylori* is introduced into the human stomach, it can be eliminated or could colonize the gastric mucosa. After gastric colonization, *H. pylori* causes acute infection or is spontaneously eliminated. In children, spontaneous eradication can occur several times until colonization takes place. It is not known whether this depends on the infectious dose of *H. pylori* strain or exposure to several strains with different characteristics [18]. Acute infection with *H. pylori* is manifested through abdominal pain and PMN infiltration in the gastric mucosa that lasts for several weeks. Subsequently, it turns into a superficial chronic gastritis with increased recruitment of lymphocytes and mononuclear cells. Superficial gastritis may or may not evolve to atrophic gastritis which may later lead to intestinal metaplasia, dysplasia and gastric cancer[19].

Antibodies expressing local immune responses are immunoglobulins of IgA, IgM and IgG class [20].In the humoral immune response, IgM-like antibodies are produced shortly after colonization, whereas IgG-type antibodies may be delayed for 3-6 months. So within a few weeks of primary exposure to *H. pylori*, the infection can be established. The secretory IgA is produced in the ischemic area of the gastric glands of the anus. By the immuno peroxidation technique it was observed that in the gastric mucosa, antibodies from the IgG and IgA classes opsonize the surface of the bacterium. IgA is dominant in the gastric secretion and protects the mucosa by interfering with bacterial adhesion to the surface of the epithelium [21].

Cellular immunity involves T lymphocytes, B lymphocytes, macrophages, basophils and mast cells[22].In the last years, it has been demonstrated that the genetic polymorphism has a critical role in gastric carcinogenesis, being involved in the inflammatory response to *H. pylori* infection, mucosal protection, anti-oxidative response, detoxification, etc. [23].

A recent study confirmed that proinflammatory IL-1RN genotypes are significantly associated with an increased risk of non-cardiac adenocarcinoma in H. pylori-positive cases [15].

Non-Hodgkin's gastric lymphoma affects the Mucosa Associated Lymphoid Tissue (MALT) lymphoid tissue. In the normal gastric mucosa, there are only a few T lymphocytes located between the epithelial cells [24]. The hypothetical mechanism by which *H. pylori* interferes with the pathogenesis of gastric lymphoma appears to be the following: chronic inflammation in response to *H. pylori* infection leads to B cell proliferation and the formation of lymphoid aggregates or follicles. 90% of cases of gastric MALT lymphoma are the consequence of *H pylori* infection., its eradication being the first step in the treatment of stage I MALT gastric lymphoma [25].

7. CONCLUSIONS

The environment, diet, *Helicobacter pylori* infections and genetic factors are involved in the pathogenesis of gastric malignancies. *H. pylori* infection is directly correlated with gastric cancer, however, the way through which the others intra-gastric bacterial species interfere with the effect of *H. pylori* in the development of gastric cancer is still undeclared.

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